REMARKS/ARGUMENTS

Applicant would like to thank the Examiner and his supervisor Examiner Wang for the courtesy extended to David Rivas, MD, Nadine Chien, Ph.D., Joe Kentoffio and the undersigned at the personal interview on June 8, 2006. During the course of the interview, the prior art rejection was discussed and in particular, the McMahon et al. reference was discussed in detail. As discussed in more detail below, Applicant's representatives made the following primary points:

- because the "as needed" use of paroxetine in McMahon et al. was not structured to avoid a priming dose effect, the study does not provide sufficient information for the skilled person to conclude that paroxetine is effective to treat premature ejaculation as needed in the absence of priming doses; and
- the McMahon et al. week 1 data cannot be relied upon by one skilled in the art as demonstrating an increase in ejaculatory latency by paroxetine over control.

Claim 37-42 and 51-54 are currently pending in the application. Each of the pending claims requires the administration of dapoxetine, or a salt thereof, for the treatment of premature ejaculation, wherein the administration is effective in the absence of priming doses of the drug.

In the final Office Action mailed October 4, 2005, the Examiner makes a single rejection of all pending claims under 35 U.S.C. §103(a) as being unpatentable over McMahon et al. (J. Urology, 161:1826-30, 1999) and Lane (J. Psychopharmacology, 11(1):72-82, 1997) in view of Eli Lilly (ZA 9300694) and Robertson et al. (U.S. Patent No. 5,135,947).

In addressing Applicant's arguments, the Examiner takes the position that McMahon et al. shows the administration of paroxetine on an as-needed basis for the treatment of premature ejaculation, wherein the administration is effective in the absence of priming doses. This position appears to be primarily based on two arguments.

The first argument underlying the rejection is based on McMahon et al.'s statement that "paroxetine as needed is significantly better if patients are initially treated with the drug daily." The Examiner posits that the skilled person would understand this statement to mean that as needed use of paroxetine without initial daily treatment is effective, even if at a lesser degree

than with initial daily treatment. From this, the Examiner concludes that administration of paroxetine in the absence of a priming dose would be effective in treating premature ejaculation. This conclusion does not logically follow. In the attached Declaration of David A. Rivas, MD under 37 CFR 1.132, Dr. Rivas concludes in ¶ 4 that *McMahon et al.'s conclusions regarding as needed dosing of paroxetine does not allow one skilled in the art to draw any conclusions about whether or not as needed use of paroxetine in the absence of priming doses is efficacious because the "as needed" use of paroxetine in McMahon et al. does not preclude priming doses.*

- McMahon et al.'s statement that initial daily treatment improves as needed efficacy of paroxetine was based on a greater mean ejaculatory latency time in Study 2 (initial daily dosing) than in Study 1 (no initial daily dosing). (McMahon et al., p. 1829, col. 1, ll. 20-25) (Rivas Decl., ¶ 4.b.);
- mean ejaculatory latency time for study Groups A-D is calculated using all data throughout the treatment phases (i.e., multiple instances of intercourse per week over 4 week treatment phases) when paroxetine had been used over a period of time (Rivas Decl., ¶ 4.c.);
- paroxetine use throughout a 4 week period, even in Study 1 without prior 2 week daily dosing, is not "in the absence of a priming dose" (Rivas Decl., ¶ 4.d.);
- the McMahon et al. study design did not impose a minimum time interval between intercourse episodes and therefore, paroxetine from one dose that was not cleared from the body could, in combination with a subsequent dose, result in paroxetine exposure in the patient greater than a single dose, thereby functioning as a priming dose (Rivas Decl., ¶ 4.e.);
- therefore, McMahon et al.'s statement that "paroxetine as needed is significantly better if patients are initially treated with the drug daily," which is based on mean ejaculatory latency time, is not relevant to whether paroxetine is effective in the absence of a priming dose because

the "as needed" use of paroxetine in McMahon et al. was not designed to avoid a priming dose effect (Rivas Decl., ¶ 4.f.).

The Examiner's position that McMahon et al. demonstrates that as needed use of paroxetine to treat premature ejaculation is effective in the absence of priming doses must be withdrawn in view of the arguments presented above and the declaration of Dr. Rivas, one skilled in the art, concluding that the McMahon et al. study does not demonstrate that as needed use of paroxetine to treat premature ejaculation is effective in the absence of a priming dose.

The Examiner's second argument underlying the rejection is based on an interpretation of McMahon et al.'s data which the Examiner characterizes as "clearly illustrat[ing] (Figure 1) that the mean ejaculatory interval was seen to increase after one week of administration of paroxetine in both Groups A and B by identical amounts and that the increase was more than that observed for placebo." The Examiner further commented that "McMahon et al. does not state that the results of week 1 are *not* statistically superior." These statements of the Examiner, demonstrating reliance on the week 1 data in support of the rejection are *contrary* to the understanding that one skilled in the art would have of the week 1 data.

In the Rivas Declaration, Dr. Rivas states in ¶ 3.b. that McMahon et al. does not provide sufficient information to determine whether the week 1 treatment data of Study 1 are statistically significantly different from the control data. Further, the fact that McMahon et al. does not state that the week 1 treatment data of Study 1 are statistically significantly different from the control data, conveys to one skilled in the art that the authors do not consider the results at week 1 to be statistically significant, and therefore, it would be inappropriate for one to conclude that the week 1 data in Study 1 are statistically significant. (Rivas Decl., ¶ 3.a.) Consequently, as one skilled in the art, Dr. Rivas would not rely on the week 1 data as demonstrating an increase in ejaculatory latency. (Rivas Decl., ¶ 3.c.)

The Examiner's reliance on the week 1 data in support of the rejection must be withdrawn in view of the arguments presented above and the declaration of Dr. Rivas concluding that it would be inappropriate to do so.

As discussed above in relation to rebuttal of the two primary arguments underlying the rejection, (1) McMahon et al. is not relevant to the question of whether as needed use of paroxetine to treat premature ejaculation is effective in the absence of priming doses because the study was not designed to address that question; and (2) the week 1 data should not be relied upon by one skilled in the art as demonstrating an increase in ejaculatory latency. In addition to these two points, there are a number of scientific and methodological issues in McMahon et al. that makes one question the results and therefore, makes it difficult to draw meaningful conclusions from the study. Specifically, as discussed in ¶ 6 of the Rivas Declaration, these issues include:

- lack of information regarding assignment of patients having primary or secondary premature ejaculation to treatment and control groups and whether bias may have been introduced because of uneven distribution of such patients (Rivas Decl., ¶ 6.a.)
- the unusual report of no side effects in the group of patients taking paroxetine as needed in Study 1 (Rivas Decl., ¶ 6.b.);
- the potential of behavior modification or bias based on a single blind, rather than a double blind study, and lack of information regarding stopwatch measurement directions (Rivas Decl., ¶ 6.c.);
- the use by McMahon et al. of different time periods for measuring pretreatment values of IELT (3 weeks) and coitus frequency (3 months) and for measuring IELT and coitus frequency during the study (weekly) (Rivas Decl., ¶ 6.d.).

In relation to the McMahon et al. reference, the Examiner addresses a number of other supporting arguments made by Applicant in the prior Amendment. The Examiner's comments will be briefly addressed here.

- The Examiner states that he did previously cite McMahon et al. for the element of "as needed" administration rather than relying on the argument of "optimization;" however, the prior Office Action stated that administration "in the dosages claimed and <u>at the times claimed</u>" would be obvious through optimization.

- The Examiner states that he relies on the "broad teaching of McMahon et al." and not on the introductory postulate that "[SSRI's] should reduce sexual excitement and have a beneficial effect on premature ejaculation" (which was based on a rat model showing serotonin inhibits sexual function) to support his conclusion that McMahon et al., in combination, would lead one skilled in the art to select dapoxetine for treatment of premature ejaculation; however, the Examiner specifically referenced the passage in making the prior rejection.
- In response to Applicant's comments concerning deficiencies in McMahon et al.'s methodology, and citing *In re Sasse*, the Examiner states that McMahon et al. is presumed to be operable for teaching the administration of SSRIs for treating premature ejaculation on an as needed basis and makes a distinction between "scientific validity" and "operability;" the Rivas Declaration addresses the methodological issues of McMahon et al. and concludes that one skilled in the art, reading McMahon et al., would not accept that the use of paroxetine to treat premature ejaculation would be operable on an as needed basis in the absence of priming doses.

In the rejection, the Examiner also relies on Lane, in addition to McMahon et al., as showing the administration of SSRIs on an as needed basis for treatment of premature ejaculation. Applicant notes that, although the Examiner states that Lane teaches administration of SSRIs on an as needed basis for treatment of premature ejaculation, the Examiner does not explicitly state that Lane teaches as needed administration that is effective in the absence of priming doses, as is currently claimed.

Further, the Examiner argues that Lane does not suggest that treatment of premature ejaculation does not work (Office Action, p. 5, ll. 21-22), but merely suggests that the dosage of the drugs used needs to be optimized to determine an acceptable level of treatment benefit. In

fact, however, Lane questions the efficacy of such treatment by stating "the efficacy of lower doses and different dosing regimens has yet to be fully explored."

Moreover, the only study mentioned by Lane referencing as needed use of an SSRI is the Swartz abstract. As previously noted, while the Swartz abstract makes reference to "as needed" dosing, it is unclear what is meant by "as needed" in this abstract because the dosing description of all patients made reference to daily usage (" a daily dose," "a regular daily schedule," or "25 mg/day dose taken on an 'as needed' schedule"). The Examiner did not address this ambiguity in Swartz.

Even if the administration in Swartz was "as needed" and not daily as his regimen descriptions suggest, the fact that all results (daily dosing and as needed) are averaged into a single result makes it impossible for a skilled person to know whether the as needed dosing was effective at all or whether non-effective results were simply averaged into a seemingly successful number. The Examiner addresses this point by stating that the averaging does not matter because Swartz "clearly teaches administration on an as needed basis." By reaching this conclusion, the Examiner seems to be saying that as long as a reference states that "as needed" dosing was attempted, regardless of whether it was successful, the reference is effective against the claims. Applicant disagrees. If a reference, as in this case, merely suggests that a particular dosing regimen was followed and does not provide sufficient information to allow the skilled person to determine whether it was successful, it cannot be said to "teach" those in the field to follow that dosing regimen.

In addition, the Swartz reference is ambiguous in regard to priming doses because it states that "[a] positive response was present after the initial dose." This statement is unclear whether a "positive response" was seen with the initial dose or whether a "positive response" was seen after the initial dose with second and subsequent doses. Further, no criteria are given for a "positive response," and the number of patients involved with the variety of dosing regimens does not allow any statistical significance to be given to these results.

The statement in Swartz that the 26-hour elimination half life of sertraline allows considerable liberties in dosing schedules has more significance in regard to the claimed

invention than the Examiner admits. The Examiner states that this comment only means that "administration schedules may be adjusted to the particular needs of a patient." Because of this relatively long half life, a given dose of sertraline will remain in the body over a long period of time. This comment, therefore, suggests that sertraline does not need to be given on an as needed basis since levels of the drug remain in the body for a long time. In addition, since the drug remains in the body for a long time, a given dose can function as a priming dose for subsequent administrations of the drug.

In view of these shortcomings, Swartz cannot be said to teach (1) as needed dosing; (2) that as needed dosing is effective; (3) the absence of priming doses; or (4) that as needed dosing in the absence of priming doses is effective. Since Swartz is the only disclosure in Lane referencing as needed use of an SSRI, Lane does not teach that the administration of SSRIs on an as needed basis for treatment of premature ejaculation is effective and (although the Examiner does not explicitly state this) Lane does not teach such as needed use that is effective in the absence of priming doses.

The Examiner argues that Applicant attacked the citation of Eli Lilly individually and not as part of the combination of cited references. In the Office Action dated 3/10/05, the Examiner cited Eli Lilly as "teach[ing] the treatment of premature ejaculation with the SSRIs fluoxetine, dapoxetine, and duloxetine." Applicant previously argued that Eli Lilly did not effectively teach the treatment of premature ejaculation with dapoxetine, precisely addressing the subject matter for which the Examiner used this reference. In the context of addressing the combination of references cited by the Examiner, since Applicant had argued that none of McMahon, Lane or Robertson taught the use of dapoxetine on an as-needed basis or effectiveness in the absence of priming doses, Applicant also noted that Eli Lilly did not teach these elements even though the Examiner did not cite the reference specifically for them.

A supplemental Information Disclosure Statement is being submitted herewith.

Based upon the foregoing, Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone

conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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